Second Primary Breast Cancer Occurrence According to Hormone Receptor Status

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Background Contralateral second primary breast cancers occur in 4% of female breast cancer survivors. Little is known about differences in risk for second primary breast cancers related to the estrogen and progesterone receptor (hormone receptor [HR]) status of the first tumor.

Methods We calculated standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for contralateral primary breast cancers among 4927 women diagnosed with a first breast cancer between January 1, 1992, and December 31, 2004, using the National Cancer Institute's Surveillance, Epidemiology, and End Results database.

Results For women whose first breast tumors were HR positive, risk of contralateral primary breast cancer was elevated, compared with the general population, adjusted for age, race, and calendar year (SIR = 2.22, 95% CI = 2.15 to 2.29, absolute risk [AR] = 13 cases per 10 000 person-years [PY]), and was not related to the HR status of the second tumor. For women whose first breast tumors were HR negative, the risk of a contralateral primary tumor was statistically significantly higher than that for women whose first tumors were HR positive (SIR = 3.57, 95% CI = 3.38 to 3.78, AR = 18 per 10 000 PY), and it was associated with a much greater likelihood of an HR-negative second tumor (SIR for HR-positive second tumors = 1.94, 95% CI = 1.77 to 2.13, AR = 20 per 10 000 PY; SIR for HR-negative second tumors = 9.81, 95% CI = 9.00 to 10.7, AR = 24 per 10 000 PY). Women who were initially diagnosed with HR-negative tumors when younger than 30 years had greatly elevated risk of HR-negative contralateral tumors, compared with the general population (SIR = 169, 95% CI = 106 to 256, AR = 77 per 10 000 PY). Incidence rates for any contralateral primary cancer following an HR-negative or HR-positive tumor were higher in non-Hispanic blacks, Hispanics, and Asians or Pacific Islanders than in non-Hispanic whites.

Conclusions Risk for contralateral second primary breast cancers varies substantially by HR status of the first tumor, age, and race and/or ethnicity. Women with HR-negative first tumors have nearly a 10-fold elevated risk of developing HR-negative second tumors, compared with the general population. These findings warrant intensive surveillance for second breast cancers in women with HR-negative tumors.

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Breast cancer is increasingly recognized to be a heterogeneous group of malignancies. Molecular profiling of breast cancers according to their gene expression has reliably classified tumors into subtypes including luminal, basal, and HER2/neu overexpressed (1–4). These molecular subtypes are approximated by combinations of the routinely measured biomarkers estrogen receptor (ER), progesterone receptor (PR), and HER2/neu: Luminal cancers are usually ER and/or PR positive, whereas basal tumors are generally ER, PR, and HER2/neu-negative, and HER2/neu-overexpressed tumors vary in their ER and PR status. Hormone receptor (HR) status of the tumor is associated with substantial variation in breast cancer incidence and mortality, which vary further by age and race and/or ethnicity (5,6). Given the need for more effectively targeted treatment and prevention, the identification of genetic and hormonal risk factors for specific molecular subtypes of breast cancer is an area of intense investigation.

Nearly one in 25 breast cancer survivors will develop a second primary breast cancer at least 6 months after her initial diagnosis (7). The risk of developing a second primary breast cancer is consistently elevated among women with a strong family history of breast cancer (8–11), including inherited *BRCA1*, *BRCA2*, or *CHEK2* mutations (12–14). Women who develop two primary breast cancers are generally younger than most women who have had only one breast cancer (7), a finding that is consistent with an inherited cancer predisposition (15,16). The study of women with two primary breast

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cancers is therefore a high-yield approach to investigate the genetic causes of breast cancer and their association with epidemiological risk factors and molecular subtypes of breast tumors (2,5).

Patterns of second primary cancer development are poorly understood in the context of breast cancer heterogeneity. To our knowledge, no large population-based study has yet investigated second primary breast cancer incidence patterns specifically according to tumor subtype, in part because of the large population needed for adequate statistical power to calculate incidence by subtype. Here, we take advantage of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, one of the largest and the highest quality databases worldwide that track sequential cancers, to describe and quantify risks of second primary breast cancer over time according to HR status and patient characteristics.

Subjects and Methods

Data Resource

We identified from the SEER program a population-based cohort of patients with an initial diagnosis of breast cancer and obtained information regarding the occurrence of subsequent primary breast cancer. Patient demographic and detailed tumor information was abstracted directly from medical records and reported to the SEER program following standard procedures. SEER data are collected according to the most stringent data quality standards of all worldwide cancer registries, including multiple audits for reporting completeness, which is estimated as at least 98% in all regions. Initially eligible for the cohort were 267 666 patients with first primary invasive breast cancer (*International Classification of Disease for Oncology, Third Revision*, sites 50.0–50.9; all histologies excluding sarcomas and lymphomas 9050–9055, 9140, 9590–9989) diagnosed between the years 1992 and 2004 in the following geographic areas: the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; the metropolitan areas surrounding Atlanta, Georgia; Detroit, Michigan; San Francisco and/or Oakland, California; Seattle and/or Puget Sound, Washington; San Jose and/or Monterey, California; Los Angeles, California; and rural Georgia for whom race and/or ethnicity and age were known and diagnosis was not based on death certificate or autopsy. We defined the following categories of tumor HR status: positive (ER or PR positive), negative (both ER and PR negative, ER negative and PR unknown, or PR negative and ER unknown), and unknown (both ER and PR unknown). A total of 48 777 patients were excluded for having unknown HR status for the first primary tumor. These patients differed from those with known HR status with respect to age, race and/or ethnicity, and year of diagnosis. Patients were further excluded for the following reasons in a hierarchical fashion: subsequent breast cancer diagnosis within 2 months of first diagnosis (n = 1172), missing follow-up time (n = 1038), or intermediate non breast tumor diagnosed between first breast tumor and second contralateral breast tumor (n = 4036).

All patients were followed up for subsequent cancers through December 31, 2005. We defined the event of interest as contralateral second primary breast cancer to restrict our assessment to tumors that could not have been recurrences of the first primary tumor, miscoded as a second ipsilateral primary breast cancer.

CONTEXT AND CAVEATS

Prior knowledge

Little has been known about whether a woman's risk of developing a second primary breast tumor is related to the hormone receptor (HR) status of the first tumor.

Study design

Data from the Surveillance Epidemiology, and End Results (SEER) registry were analyzed for 4927 women who were first diagnosed with breast cancer between 1992 and 2004 and subsequently developed contralateral second primary breast cancers. Incident cases, standardized incidence ratios, and absolute risks were determined as a function of HR status and either time to second tumor, calendar year, or the patient's age or race.

Contribution

Women who had survived HR-positive breast cancers had more than a twofold increased risk of a second primary tumor, and women who had survived HR-negative breast cancers had nearly a fourfold increased risk, compared with the age-, race-, and year-adjusted general population. Those with HR-negative first tumors were much more likely to develop HR-negative second tumors, and this was especially true for women first diagnosed before age 30, who had 169 times the normal risk of a second HR-negative tumor.

Implications

Women who have had breast cancer should be more intensively screened for the appearance of second tumors, particularly if the first tumors were HR negative and/or if the women were first diagnosed at less than 30 years of age.

Limitations

The available data did not allow analysis by additional tumor markers nor by family history, inherited mutations, or treatment details including tamoxifen use.

From the Editors

Statistical Analysis

We used SEER*Stat version 6.3.6 (National Cancer Institute, Bethesda, MD) to calculate absolute risk (AR) and absolute excess risk (cases per 10 000 person-years [PYs]), standardized incidence ratios (SIRs), and the corresponding 95% confidence intervals (CIs) for case categories defined by HR status of the first and second tumors. SEER*Stat calculates observed (O) and expected (E) numbers of second primary cancers, the latter based on SEER breast cancer incidence rates applied to the total PYs of follow-up, weighted appropriately for cohort distributions of race and/or ethnicity, attained age, and attained calendar year. Thus, E represents the total number of cancers that would have been expected in a "general population" similar to the first primary breast cancer patients with respect to race and/or ethnicity, age, and follow-up time. The SIR is a relative risk measure representing the ratio of O to E (O/E), whereas the AR measures the yearly rate (O/PY), and the absolute excess risk measures the rate of excess cancers (O − E/PY).

We calculated AR and SIRs for contralateral second breast cancers during specified time periods of follow-up after diagnosis of the first cancer (2–59, 60–119, and ≥120 months). Within categories defined by HR status, analyses were stratified by demographic

and tumor characteristics, including race and/or ethnicity (categorized as non-Hispanic white, Hispanic, non-Hispanic black, non-Hispanic Asian, or Pacific Islander) and age (groups stratified by 10-year intervals starting at <30 years and extending to ≥70 years). Mixed-race individuals were classified according to a single race by the cancer registries. Women from Middle Eastern backgrounds were generally classified as non-Hispanic whites, and women from the Indian subcontinent were grouped with non-Hispanic Asian or Pacific Islanders. Differences in SIRs were considered statistically significant if all values within the 95% confidence interval of the first SIR did not overlap with any value within the 95% confidence interval of the second SIR.

Results

Second Primary Breast Cancers by Time Since Diagnosis

The analysis was based on 4927 women with contralateral second primary breast cancer. Of these, 3701 had a first HR-positive tumor and 1226 had a first HR-negative tumor. The risk of a new contralateral primary breast cancer among women who had a breast cancer of any HR status was more than two fold (SIR = 2.46, 95% CI = 2.40 to 2.52) that of the general population. Risk of a second breast cancer was then stratified by HR status and time since initial diagnosis (Table 1).

For women with a first HR-positive breast cancer, risks of an HR-positive and an HR-negative second tumor were similar, and the average risk of developing a second tumor was approximately double the risk of a first primary breast cancer in an unaffected woman (SIR = 2.22, 95% CI = 2.15 to 2.29, AR = 13 cases per 10000 PYs). For women whose second tumor was also HR positive, the risk was slightly but not statistically significantly higher for developing the second tumor 5–9 years (SIR = 2.29, 95% CI = 2.14 to 2.46, AR = 30 per 10000 PY) and 10 years or more (SIR = 2.51, 95% CI = 2.14 to 2.94, AR = 34 per 10000 PY) following diagnosis, compared with the first 5 years after diagnosis (SIR = 2.05, 95% CI = 1.95 to 2.15, AR = 24 per 10000 PY). Otherwise, the risk of second tumors was equivalent across HR status of the second tumor and time since diagnosis.

By contrast, among women with a first HR-negative breast cancer, overall risk of any second primary breast cancer was substantially higher (SIR = 3.57, 95% CI = 3.38 to 3.78, AR = 18 per 10000 PY) than for women with a first HR-positive cancer, and this risk varied markedly by the HR status of the second tumor. Across the entire follow-up period, risk of a second HR-negative tumor (SIR = 9.81, 95% CI = 9.00 to 10.7, AR = 24 per 10000 PY) was five times higher than the risk of a second HR-positive tumor (SIR = 1.94, 95% CI = 1.77 to 2.13, AR = 20 per 10000 PY).

Second Primary Breast Cancers by Calendar Year

We next analyzed risks for second primary breast cancer by HR status, age, and calendar year of diagnosis (Table 2). For women who were first diagnosed with an HR-positive tumor when younger than 50 years, risk of any second primary breast cancer was statistically significantly higher (for 1992–1996: SIR = 3.51, 95% CI = 3.19 to 3.85, AR = 12 per 10000 PY) than that for women who were first diagnosed with an HR-positive tumor at age 50 years or older (for 1992–1996: SIR = 2.11, 95% CI = 2.00 to 2.21, AR = 15 per 10000

Table 1. Absolute risk per 10000 person-years, observed incident cases, and standardized incidence ratios with 95% confidence intervals of contralateral second primary breast cancers, by hormone receptor status of the first primary tumor and time since diagnosis*

	Time since primary diagnosis											
	2–59 mo			60–119 mo			≥120 mo			Total		
Breast cancer history	AR	O	SIR† (95% CI)	AR	O	SIR† (95% CI)	AR	O	SIR† (95% CI)	AR	O	SIR† (95% CI)
First primary HR-positive												
Second primary HR-positive	24	1551	2.05 (1.95 to 2.15)	30	799	2.29 (2.14 to 2.46)	34	157	2.51 (2.14 to 2.94)	26	2507	2.15 (2.06 to 2.23)
Second primary HR-negative	5	346	2.20 (1.98 to 2.45)	6	150	2.16 (1.83 to 2.53)	7	32	2.64 (1.80 to 3.72)	6	528	2.21 (2.03 to 2.41)
Second primary HR unknown	8	499	2.77 (2.53 to 3.03)	5	143	2.00 (1.69 to 2.36)	5	24	1.97 (1.26 to 2.92)	7	666	2.53 (2.34 to 2.73)
All second primary tumor types	13	2396	2.19 (2.10 to 2.28)	14	1092	2.23 (2.10 to 2.37)	15	213	2.45 (2.14 to 2.81)	13	3701	2.22 (2.15 to 2.29)
First primary HR-negative												
Second primary HR-positive	18	271	1.82 (1.61 to 2.05)	24	152	2.15 (1.82 to 2.52)	27	33	2.19 (1.51 to 3.08)	20	456	1.94 (1.77 to 2.13)
Second primary HR-negative	23	351	9.85 (8.84 to 10.9)	25	156	9.77 (8.30 to 11.4)	26	32	9.70 (6.63 to 13.7)	24	539	9.81 (9.00 to 10.7)
Second primary HR unknown	13	189	5.20 (4.48 to 6.00)	6	36	2.51 (1.76 to 3.48)	5	6	2.10 (0.77 to 4.57)	10	231	4.31 (3.78 to 4.91)
All second primary tumor types	18	811	3.67 (3.42 to 3.93)	18	344	3.41 (3.06 to 3.79)	19	71	3.35 (2.62 to 4.22)	18	1226	3.57 (3.38 to 3.78)

* HR status was defined as follows: positive (ER or PR positive), negative (both ER and PR negative, ER negative and PR unknown, or PR negative and ER unknown), and unknown (both ER and PR unknown). AR = absolute risk; O = observed incident cases; SIR = standardized incidence ratio; CI = confidence interval; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor.

† Expected numbers of second primary cancers were based on Surveillance, Epidemiology, and End Results breast cancer incidence rates applied to the total person-years of follow-up, weighted appropriately for cohort distributions of race and/or ethnicity, attained age, and attained calendar year.

Table 2. Absolute risk per 10 000 person-years, observed incident cases, and standardized incidence ratio with 95% confidence interval of contralateral second primary breast cancer, by hormone receptor status, age, and calendar year*

	1992–1996			1997–2000			2001–2004		
Breast cancer history	**AR**	**O**	**SIR† (95% CI)**	**AR**	**O**	**SIR† (95% CI)**	**AR**	**O**	**SIR† (95% CI)**
Women with first primary tumor at age <50 y and HR-positive									
Second primary HR-positive	22	274	3.24 (2.87 to 3.65)	21	166	3.51 (2.99 to 4.08)	18	67	3.38 (2.62 to 4.29)
Second primary HR-negative	7	84	3.31 (2.64 to 4.10)	5	42	2.89 (2.08 to 3.91)	5	19	3.10 (1.87 to 4.84)
Second primary HR unknown	8	93	5.01 (4.04 to 6.14)	6	45	5.19 (3.79 to 6.95)	5	20	5.99 (3.66 to 9.25)
All second primary tumor types	12	451	3.51 (3.19 to 3.85)	11	253	3.59 (3.16 to 4.06)	10	106	3.62 (2.96 to 4.38)
Women with first primary tumor at age ≥50 y and HR-positive									
Second primary HR-positive	30	1067	2.09 (1.97 to 2.22)	26	624	1.80 (1.66 to 1.94)	27	309	1.95 (1.74 to 2.18)
Second primary HR-negative	6	197	2.09 (1.81 to 2.41)	5	129	1.93 (1.61 to 2.30)	5	57	1.80 (1.36 to 2.33)
Second primary HR unknown	8	287	2.18 (1.93 to 2.45)	6	150	2.09 (1.77 to 2.45)	6	71	2.39 (1.87 to 3.01)
All second primary tumor types	15	1551	2.11 (2.00 to 2.21)	12	903	1.86 (1.74 to 1.98)	13	437	1.99 (1.81 to 2.19)
Women with first primary tumor at age <50 y and HR-negative									
Second primary HR-positive	19	91	3.18 (2.56 to 3.91)	16	42	3.00 (2.16 to 4.05)	7	9	1.54 (0.71 to 2.93)
Second primary HR-negative	34	160	17.15 (14.6 to 20.0)	36	96	20.30 (16.4 to 24.8)	36	45	22.28 (16.3 to 29.8)
Second primary HR unknown	13	60	8.94 (6.82 to 11.5)	12	31	11.27 (7.66 to 16.0)	10	12	11.43 (5.91 to 20.0)
All second primary tumor types	22	311	6.97 (6.21 to 7.79)	21	169	7.86 (6.72 to 9.14)	18	66	7.42 (5.74 to 9.43)
Women with first primary tumor at age ≥50 y and HR-negative									
Second primary HR-positive	24	171	1.74 (1.49 to 2.02)	21	95	1.62 (1.31 to 1.98)	21	48	1.65 (1.21 to 2.18)
Second primary HR-negative	14	99	4.99 (4.06 to 6.08)	22	98	7.90 (6.41 to 9.62)	18	41	6.20 (4.45 to 8.41)
Second primary HR unknown	9	68	2.70 (2.09 to 3.42)	11	47	3.83 (2.82 to 5.10)	6	13	2.34 (1.25 to 4.01)
All second primary tumor types	16	338	2.36 (2.11 to 2.62)	18	240	2.88 (2.53 to 3.27)	15	102	2.47 (2.01 to 3.00)

* HR status was defined as follows: positive (ER or PR positive), negative (both ER and PR negative, ER negative and PR unknown, or PR negative and ER unknown), and unknown (both ER and PR unknown). AR = absolute risk; O = observed incident cases; SIR = standardized incidence ratio; CI = confidence interval; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor.

† Expected numbers of second primary cancers were based on Surveillance, Epidemiology, and End Results breast cancer incidence rates applied to the total person-years of follow-up, weighted appropriately for cohort distributions of race and/or ethnicity, attained age, and attained calendar year.

PY); the pattern was similar across periods. During all periods, the risk of second tumors of unknown HR status was generally higher than the risk of either HR-positive or HR-negative second tumors among women who were first diagnosed younger than 50 years. For women diagnosed at age 50 years and older with a first HR-positive tumor, the overall risk of a second breast tumor and the risk of a second HR-positive tumor were both greater in 1992–1996 than in 1997–2000, but this trend did not persist in 2001–2004.

Women who were first diagnosed with an HR-negative tumor when younger than 50 years had a higher risk for any second primary breast cancer (for 1992–1996: SIR = 6.97, 95% CI = 6.21 to 7.79, AR = 22 per 10 000 PY) than women who were first diagnosed with an HR-negative tumor at age 50 years or older (for 1992–1996: SIR = 2.36, 95% CI = 2.11 to 2.62, AR = 16 per 10 000 PY). Women with a first HR-negative breast cancer had higher risk for a second HR-negative cancer across all calendar years and ages. Risks for a second HR-negative cancer were highest in women initially diagnosed when younger than 50 years (for 1992–1996: SIR = 17.2, 95% CI = 14.6 to 20.0, AR = 34 per 10 000 PY).

Second Primary Tumors by Age at Diagnosis

We next analyzed risks for second primary breast cancers according to HR status and age at first cancer diagnosis (Table 3). For women with a first HR-positive tumor, there was an inverse trend with age at diagnosis, with risk of any second primary cancer highest when cancer was first diagnosed before age 30 years (SIR = 43.8, 95% CI = 27.1 to 66.9, AR = 19 per 10 000 PY), declining statistically significantly for age 30–39 years (SIR = 7.39, 95% CI = 6.37 to 8.53, AR = 13 per 10 000 PY) and dropping to SIRs between 1.0 and 3.0 thereafter. This trend by age was observed irrespective of HR status of the second tumor.

For women with a first HR-negative tumor, risks were exceedingly pronounced among younger patients. If an HR-negative tumor was initially diagnosed when the patient was younger than 30 years, the SIR of any second primary tumor was 79.5 (95% CI = 54.0 to 113, AR = 36 per 10 000 PY). Also, by contrast to the HR-positive group, women whose first tumors were HR negative had a statistically significantly greater risk of a second HR-negative cancer than of a second HR-positive cancer. This difference persisted across all ages at diagnosis but was particularly marked for women first diagnosed when younger than 30 years (SIR = 169, 95% CI = 106 to 256, AR = 77 per 10 000 PY for HR negative vs SIR = 20.0, 95% CI = 5.45 to 51.2, AR = 14 per 10 000 PY for HR positive) and at age 30–39 years (SIR = 35.3, 95% CI = 28.9 to 42.7, AR = 42 per 10 000 PY for HR negative vs SIR = 5.22, 95% CI = 3.73 to 7.11, AR = 16 per 10 000 PY for HR positive).

Second Primary Breast Cancers by Patient Race and/or Ethnicity

We then analyzed the risks for second primary breast cancer by HR status and race and/or ethnicity (Table 4). Among women with a first HR-positive breast cancer, risks of any second primary

Table 3. Absolute risk per 10 000 person-years, observed incident cases, and standardized incidence ratios with 95% confidence intervals of contralateral second primary breast cancers, by hormone receptor status and age*

Patient classification	AR	O	SIR (95% CI)
First primary HR-positive			
Second primary HR-positive, age (y)			
<30	22	8	30.8 (13.3 to 60.6)
30–39	21	101	6.25 (5.09 to 7.60)
40–49	21	398	2.94 (2.66 to 3.24)
50–59	23	523	1.98 (1.81 to 2.15)
60–69	33	719	2.10 (1.95 to 2.26)
≥70	29	758	1.85 (1.72 to 1.99)
Second primary HR-negative, age (y)			
<30	17	6	37.5 (13.8 to 81.6)
30–39	10	47	7.95 (5.84 to 10.6)
40–49	5	92	2.30 (1.86 to 2.82)
50–59	6	132	2.06 (1.72 to 2.44)
60–69	6	136	2.14 (1.80 to 2.53)
≥70	4	115	1.77 (1.46 to 2.13)
Second primary HR unknown, age (y)			
<30	19	7	117 (46.9 to 240)
30–39	8	40	11.8 (8.45 to 16.1)
40–49	6	111	4.09 (3.37 to 4.93)
50–59	6	138	2.70 (2.27 to 3.19)
60–69	7	162	2.26 (1.92 to 2.63)
≥70	8	208	1.88 (1.64 to 2.16)
All second primary tumor types, age (y)			
<30	19	21	43.8 (27.1 to 66.9)
30–39	13	188	7.39 (6.37 to 8.53)
40–49	11	601	2.97 (2.74 to 3.22)
50–59	12	793	2.09 (1.95 to 2.24)
60–69	15	1017	2.13 (2.00 to 2.27)
≥70	14	1081	1.85 (1.74 to 1.96)
First primary HR-negative			
Second primary HR-positive, age (y)			
<30	14	4	20.0 (5.45 to 51.2)
30–39	16	40	5.22 (3.73 to 7.11)
40–49	17	98	2.41 (1.96 to 2.94)
50–59	17	99	1.49 (1.21 to 1.82)
60–69	25	105	1.69 (1.38 to 2.05)
≥70	29	110	1.90 (1.57 to 2.30)
Second primary HR-negative, age (y)			
<30	77	22	169 (106 to 256)
30–39	42	106	35.3 (28.9 to 42.7)
40–49	29	173	13.4 (11.4 to 15.5)
50–59	20	121	7.01 (5.81 to 8.37)
60–69	15	62	5.12 (3.92 to 6.56)
≥70	14	55	5.82 (4.38 to 7.58)
Second primary HR unknown, age (y)			
<30	17	5	83.3 (27.1 to 194)
30–39	12	30	17.7 (11.9 to 25.2)
40–49	12	68	7.76 (6.03 to 9.84)
50–59	8	48	3.53 (2.60 to 4.68)
60–69	9	38	2.80 (1.98 to 3.84)
≥70	11	42	2.66 (1.91 to 3.59)
All second primary tumor types, age (y)			
<30	36	31	79.5 (54.0 to 113)
30–39	23	176	14.2 (12.2 to 16.5)
40–49	19	339	5.44 (4.88 to 6.05)
50–59	15	268	2.76 (2.44 to 3.11)
60–69	16	205	2.33 (2.03 to 2.68)
≥70	18	207	2.49 (2.17 to 2.86)

* HR status was defined as follows: positive (ER or PR positive), negative (both ER and PR negative, ER negative and PR unknown, or PR negative and ER unknown), and unknown (both ER and PR unknown). AR = absolute risk; O = observed incident cases; SIR = standardized incidence ratio; CI = confidence interval; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor.

Table 4. Absolute risk per 10 000 person-years, observed incident cases, and standardized incidence ratios with 95% confidence intervals of contralateral second primary breast cancers, by hormone receptor status and race and/or ethnicity*

Patient classification	AR	O	SIR (95% CI)
First primary tumor HR-positive			
Second primary HR-positive			
NH white	27	2020	1.97 (1.89 to 2.06)
NH black	26	155	3.37 (2.86 to 3.94)
Hispanic	24	146	3.56 (3.01 to 4.19)
NH Asian or Pacific Islander	25	186	3.28 (2.82 to 3.78)
Second primary HR-negative			
NH white	5	406	2.10 (1.90 to 2.31)
NH black	9	52	2.55 (1.90 to 3.34)
Hispanic	6	34	2.97 (2.06 to 4.15)
NH Asian or Pacific Islander	5	36	2.71 (1.90 to 3.76)
Second primary HR unknown			
NH white	7	510	2.31 (2.11 to 2.52)
NH black	10	61	3.51 (2.69 to 4.51)
Hispanic	9	53	3.87 (2.90 to 5.06)
NH Asian or Pacific Islander	6	42	3.61 (2.60 to 4.88)
All second primary tumor types			
NH white	13	2936	2.04 (1.97 to 2.12)
NH black	15	268	3.20 (2.83 to 3.61)
Hispanic	13	233	3.52 (3.08 to 4.00)
NH Asian or Pacific Islander	12	264	3.23 (2.85 to 3.65)
First primary tumor HR-negative			
Second primary HR-positive			
NH white	22	352	1.84 (1.65 to 2.04)
NH black	15	42	2.18 (1.57 to 2.95)
Hispanic	14	27	2.46 (1.62 to 3.57)
NH Asian or Pacific Islander	19	35	2.75 (1.92 to 3.82)
Second primary HR-negative			
NH white	20	328	8.42 (7.54 to 9.39)
NH black	40	112	11.7 (9.65 to 14.1)
Hispanic	35	68	20.2 (15.7 to 25.6)
NH Asian or Pacific Islander	17	31	10.1 (6.88 to 14.4)
Second primary HR unknown			
NH white	9	141	3.52 (2.96 to 4.15)
NH black	13	37	5.16 (3.63 to 7.11)
Hispanic	19	38	10.3 (7.29 to 14.1)
NH Asian or Pacific Islander	8	15	5.75 (3.22 to 9.48)
All second primary tumor types			
NH white	17	821	3.03 (2.83 to 3.25)
NH black	22	191	5.31 (4.58 to 6.12)
Hispanic	23	133	7.37 (6.17 to 8.73)
NH Asian or Pacific Islander	15	81	4.40 (3.50 to 5.47)

* HR status was defined as follows: positive (ER or PR positive), negative (both ER and PR negative, ER negative and PR unknown, or PR negative and ER unknown), and unknown (both ER and PR unknown). NH = non-Hispanic; AR = absolute risk; O = observed incident cases; SIR = standardized incidence ratio; CI = confidence interval; HR = hormone receptor; ER = estrogen receptor; PR = progesterone receptor.

breast tumor were higher among non-Hispanic blacks (SIR = 3.20, 95% CI = 2.83 to 3.61, AR = 15 per 10 000 PY), Hispanics (SIR = 3.52, 95% CI = 3.08 to 4.00, AR = 13 per 10 000 PY), and non-Hispanic Asians or Pacific Islanders (SIR = 3.23, 95% CI = 2.85 to 3.65, AR = 12 per 10 000 PY) than among non-Hispanic whites (SIR = 2.04, 95% CI = 1.97 to 2.12, AR = 13 per 10 000 PY); this racial or ethnic difference persisted for HR-positive and HR-unknown second primary tumors, but no differences were observed between racial or ethnic groups for HR-negative second primary tumors. Within each racial or ethnic group, there were no

statistically significant differences in risk by HR status, with the exception of slightly increased risk of HR-unknown compared with HR-positive second primary tumors among non-Hispanic whites.

For women with a first HR-negative breast cancer, non-Hispanic blacks (SIR = 5.31, 95% CI = 4.58 to 6.12, AR = 22 per 10 000 PY), Hispanics (SIR = 7.37, 95% CI = 6.17 to 8.73, AR = 23 per 10 000 PY), and non-Hispanic Asians or Pacific Islanders (SIR = 4.40, 95% CI = 3.50 to 5.47, AR = 15 per 10 000 PY) had a higher risk of any second primary tumor than did non-Hispanic whites (SIR = 3.03, 95% CI = 2.83 to 3.25, AR = 17 per 10 000 PY); moreover, non-Hispanic blacks (SIR = 11.7, 95% CI = 9.65 to 14.1, AR = 40 per 10 000 PY) and Hispanics (SIR = 20.2, 95% CI = 15.7 to 25.6, AR = 35 per 10 000 PY) had a higher risk of a second HR-negative tumor than did non-Hispanic whites (SIR = 8.42, 95% CI = 7.54 to 9.39, AR = 20 per 10 000 PY). In all racial or ethnic groups, women with a first HR-negative cancer had a substantially higher risk of HR-negative than of HR-positive second cancer.

Discussion

To our knowledge, this SEER-based analysis is the first large, population-based study of contralateral second primary breast cancers by HR status. Previous studies have evaluated epidemiological and demographic factors associated with second primary breast cancer development (7,11,17–21), and HR status has been assessed in clinical series (22–24). In this study, we found several important risk patterns. Most notably, we documented very high relative risks of a second HR-negative tumor among women with first HR-negative tumors; although risks were extremely high among young women (160-fold), substantially elevated risks (nine-fold) were observed across all age groups. In absolute terms, this translated into an annual excess risk of 537 cases per 10 000 PYs for women diagnosed with a first HR-negative breast cancer when younger than 30 years and two cases per 10 000 PYs for women diagnosed with HR-negative breast cancers across all age groups. Women whose first HR-negative tumor occurred before age 40 years also had elevated risks of second HR-positive and HR-unknown cancers. By contrast, risks of second primary tumors among women with a first HR-positive tumor were substantially lower and fell in the twofold range for the whole cohort, although they were as high as 40-fold for women who were first diagnosed before age 30 years.

We found a strong trend in second primary breast cancer risk according to age at first diagnosis; risk of a second HR-negative primary cancer peaked in women diagnosed with a first HR-negative cancer in their twenties and thirties. Prior studies, including some using SEER data, have also noted this elevated risk of a second primary cancer with younger age at initial diagnosis (7,25). Early age at onset is a hallmark of hereditary breast cancers, particularly those associated with germline mutations in *BRCA1*, *BRCA2*, and *TP53*; approximately 8%–10% of women diagnosed with breast cancer before age 40 years carry mutations in *BRCA1* or *BRCA2* (13,15,16,26). Among *BRCA1* and *BRCA2* mutation carriers, earlier age at initial cancer onset is associated with a higher risk of contralateral breast cancer (14,27). Thus, our observation of very high risks of contralateral cancer in patients younger than 40 years is consistent with an inherited genetic basis for such risk.

However, our observed differences in risk magnitude by HR status of the first primary tumor require further explanation. Because 60%–90% of *BRCA1*-associated breast cancers are HR negative (28–32), some of the women who first present with HR-negative breast cancer before age 40 years and have a 30- to 160-fold risk for a second HR-negative cancer are likely to be *BRCA1* mutation carriers. This estimation would be consistent with a report that *BRCA1* and *BRCA2* mutation carriers often have concordant HR status between their first and second breast tumors (33). However, *BRCA1* and *BRCA2* mutations are rare in the general population, with an estimated frequency of one in 400 US women (34–36); many families with multiple, early-onset breast cancers test negative for such mutations. Other cancer susceptibility genes as yet to be identified may also play a role, either in the absence or presence of a *BRCA1* mutation. Recent investigations have reported that breast cancer stem cells have an HR-negative phenotype (37,38); women with HR-negative breast cancer may be predisposed to carcinogenesis early in the breast cell maturation process, with malignancy arising repeatedly from an HR-negative stem cell. By contrast, we observed that women younger than 40 years whose first breast cancer was HR positive had a lower risk of any second primary breast cancer. Some of these women may carry mutations in *BRCA2*. Mutations in *BRCA2* convey lower breast cancer risk and are more frequently associated with an HR-positive breast cancer phenotype compared with *BRCA1* mutations (14,26,32). Other women might carry mutations in less penetrant cancer susceptibility genes such as *CHEK2* or *PALB2* (39,40).

The risk of second primary breast tumors varied by race and ethnicity. Non-Hispanic blacks, Hispanics, and non-Hispanic Asian or Pacific Islander patients had a slightly greater risk of developing any second primary breast cancer compared with non-Hispanic whites, regardless of the HR status of the first tumor. Non-Hispanic blacks and Hispanics with a first HR-negative tumor also had substantially higher risks of a second HR-negative primary tumor than did non-Hispanic whites. Multiple publications have reported elevated rates of ER-negative, PR-negative, and HER2/neu-negative (triple negative) breast cancer in non-Hispanic black women (5,6,41). One population-based study found a high prevalence of *BRCA1* mutations, which predispose to triple-negative tumors, in Hispanic and young non-Hispanic black breast cancer patients (34). A population-based study of Asian Americans showed few differences in breast cancer HR status compared with non-Hispanic whites (41); non-Hispanic Asians or Pacific Islanders have a relatively low prevalence of *BRCA1*, but possibly a higher prevalence of *BRCA2* mutations (34,42). Causes for the observed racial and ethnic variation in risk of second primary breast cancers are likely multifactorial, involving genetic, environmental, and clinical factors. The lower risk for a second HR-positive primary cancer among non-Hispanic whites compared with other racial and ethnic groups may also reflect disparities in the ability to afford medical care, with non-Hispanic whites more able than others to afford therapy with tamoxifen or an aromatase inhibitor for a first HR-positive tumor.

We did not observe important differences in second primary breast cancer risk according to time since first diagnosis or calendar

year. The stable SIRs over a 2- to more than 120-month period suggest relatively consistent risks of second primary breast cancer, be they related to genetic or environmental triggers. Changes in risk by calendar year might be anticipated, given the recently increasing use of endocrine therapies for initial HR-positive breast cancer, which reduce the incidence of second HR-positive primary tumors (22,24,43–45). Moreover, more sensitive approaches to screening the contralateral breast, such as magnetic resonance imaging (MRI), might increase the detection of synchronous or metachronous second primary tumors (46,47). These recent management trends may have opposing effects on the incidence of second primary breast cancers, effectively canceling each other out. Alternatively, our follow-up time since the adoption of such strategies may have been too short to detect their impact.

Although this study used a large, population-based database, affording greater statistical power and more representative results than the previous smaller series, some limitations warrant consideration. The absence of SEER information on tumor HER2/neu amplification did not allow us to characterize tumors additionally by this molecular alteration, which has major implications for clinical treatment and prognosis. HER2/neu data were not recorded by the SEER registry during all years under study but are being collected now. The lack of available SEER information on family cancer history, established breast cancer risk factors, inherited genetic mutations, and treatment details for the first breast tumor limited our ability to characterize risk associated with second primary breast cancers. Of particular note, we were not able to characterize risk of second primary cancers according to adjuvant tamoxifen use among women with an HR-positive first primary cancer. Risks of second primary HR-positive tumors are lower among women receiving tamoxifen than among women receiving placebo (24). Thus, our estimates for women with first HR-positive tumors represent population-averaged risk across categories of women with heterogeneous exposure to tamoxifen. Missing HR data for first and second tumors, which differed slightly by patient race and/or ethnicity, also limited our comparisons by HR status. However, in sensitivity analyses (data not shown), recoding unknown ER or PR status as either positive or negative did not substantially alter our results. With increasingly complete ascertainment of ER, PR, and HER2/neu status in the SEER registry, future analyses of the SEER database should further enhance understanding of the epidemiology of second primary breast cancers.

Our finding that women with a first HR-negative tumor have a nearly 10-fold elevated risk of a second contralateral HR-negative breast cancer has important implications for clinical management. Currently, guidelines of the American Cancer Society recommend intensive breast screening with yearly MRI for women at increased risk of developing breast cancer (47). In this context and in light of reports that standard mammography has low sensitivity for detecting HR-negative tumors (48), our findings, if confirmed, suggest that women diagnosed with an HR-negative breast cancer would benefit from MRI-based breast screening. Future research should focus on identifying genetic factors that predispose women to multiple HR-negative tumors to target screening, prevention, and treatment strategies more effectively.

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